ORIGINAL ARTICLES

Scientific and General

SULFATHIAZOLE REACTIONS IN TOXIC AND NONTOXIC INDIVIDUALS*

R. C. GREEN, M. D.
MAJOR, M.C., U. S. ARMY
M. L. STECKEL, M. D.
CAPTAIN, M.C., U. S. ARMY
AND
JOHN M. MICHENER, M. D.
CAPTAIN, M.C., U. S. ARMY
Camp Haan

SINCE sulfathiazole has been so effective in the treatment of various infectious conditions at the Station Hospital, Camp Haan, California, its undesirable side effects have become of increasing interest and importance to us. We had observed that these side effects seemed to occur most frequently in patients who were toxic and febrile from their illness and were apparently less common in the individual whose disease did not cause a toxic, febrile response, irrespective of the total sulfathiazole dosage or its length of administration.

In an effort to substantiate or disprove this observation, hospital records of the last 300 patients to receive a single course of sulfathiazole on all services at this hospital were reviewed. Cases where two or more courses of sulfathiazole had been administered with intervening intervals were purposely excluded from this series. Numerous such cases were encountered but were omitted due to our interest in the recent work of Lyons and Balberor,[1] and others.[2] We propose to report the incidence and our conception of the mechanism of sulfathiazole side effects in these cases at a later date.

These 300 cases differ somewhat from others previously reported[3] in that all patients were men, predominantly young and vigorous. The age range was from 18 to 52 years, with a mean of 25.1 years. It was found in these cases that side effects attributable to sulfathiazole occurred approximately five times more often in toxic, febrile individuals than in the atoxic, afebrile, with due consideration also being given to total drug dosage and its length of administration.

Sulfathiazole blood levels will not be cited in any of the cases here reported since no excessive concentrations were encountered and it seems generally accepted[4] that blood concentration is not important in the production of sulfathiazole side effects.

* From the Medical Service, Station Hospital, Camp Haan, California.
Grateful acknowledgment is extended to Colonel C. Blance, M.C., Commanding; Major B. H. Henning, M.C., Chief of Surgery; Major G. A. Williamson, M.C., Chief of Orthopedics; Major W. B. Brown, M.C., Registrar, and other Staff Members for their coöperation in obtaining records used to compile this report.

COMPARISON OF "TOXIC" AND "ATOXIC" CASES

Upon segregating these cases into so-called "toxic" and "atoxic" groups, we were agreeably surprised to find them almost equal in number and that there was no appreciable difference in the average age, the "toxic" being 25 and the "atoxic" 25.2 years. There were 149 toxic, febrile individuals and 151 who had had no fever or appreciable toxic response to their disease, either immediately preceding or throughout their hospital stay. All of the so-called "toxic" cases exhibited some form of acute inflammation, and since MacCallum[5] states that probably every inflammation is accompanied by some general disturbance, such as fever, the presence of an appreciable degree and extent of fever was taken as an index of toxicity existing from the disease present. Cases were therefore arbitrarily placed in a group called "toxic" when fever from the disease of 100° F. or more persisting for two or more days, or of 99.6° F. persisting for four or more days had been experienced. All others were placed in a second group called "atoxic," although we are aware that toxicity may exist without the presence of fever.

Table 1 shows the composition of these two groups, with conditions causing hospitalization and sulfathiazole administration. This study was attempted to identify persons showing evidence of drug intoxication, no thought being given to the existence of proper indications for its administration.

Thirty patients (10 per cent) experienced undesirable reactions from the sulfathiazole, three each exhibiting two different side effects. No deaths attributable to the drug occurred among the entire 300 cases. Table 2 summarizes these side effects as to type and the group in which they occurred.

It is thus apparent that 83 per cent of those patients experiencing undesirable effects were in the so-called "toxic" group, while but 17 per cent were in the so-called "atoxic" group; or expressed in a different manner, 17.4 per cent of the 149 "toxic" patients showed evidence of drug intolerance, while but 3.3 per cent of the 151 "atoxic" exhibited similar effects. Before these figures might be assumed to be significant, it was felt that drug dosage and length of its administration should be compared in the two groups; and upon such comparison it was found that the average "toxic" patient had received 20.5 gm. of sulfathiazole over an average period of 4.9 days. The lowest total dosage was 5 gm. and the highest 71 gm. The shortest time of administration was one day, and the longest 16 days. On the other hand, the average "atoxic" individual had received 25.3 gm. of sulfathiazole over an average period of 7.3 days; the smallest total dose being 5 gm. and the greatest being 101 gm. The shortest period of administration was two days and the longest 35 days.

Thus the average "toxic" patient received 25 per cent less sulfathiazole over a 33⅓ per cent

shorter period of time than did the "atoxic" patient, yet developed five times as many undesirable effects from its use.

ANALYSIS OF PATIENTS EXHIBITING SIDE EFFECTS

This discussion might now have some significance in its relation to the side effects observed in all thirty patients, but definite conclusions cannot be reached without further analysis.

the production of its side effects. We believe that other factors besides dosage and length of administration play a part in their causation. Hendricks[4] appears to confirm this view by his statement that the number and severity of the anemias occurring among his patients given sulfonamide compounds were not dependent upon the total dosage received, the duration of treatment or the blood concentration.

TABLE 1.—*Condition Causing Hospitalization and Sulfathiazole Administration, Placed in "Toxic" or "Atoxic" Groups*

"TOXIC GROUP"*		"ATOXIC GROUP"*	
Upper respiratory infections, acute	34 cases	Gonorrhea	45 cases
Postoperative abdominal	23 cases	Abscess, minor, localized	25 cases
Lobar pneumonia	21 cases	Sinusitis, chronic	15 cases
Bronchitis, acute	20 cases	Otitis media, chronic	15 cases
Broncho-pneumonia	17 cases	Urethritis, nonspecific	13 cases
Cellulitis	9 cases	Prostatitis, chronic	6 cases
Postoperative compound fractures and other operative orthopedic conditions	7 cases	Cystitis, chronic	4 cases
Prostatitis, acute	4 cases	Postoperative compound fractures and other orthopedic cases, operative	4 cases
Epididymitis, acute	4 cases	Balanitis	3 cases
Sinusitis, acute	4 cases	Pustular dermatoses	3 cases
Otitis media, acute	3 cases	Postoperative abdominal	3 cases
Lymphangitis, acute	2 cases	Chancroid	1 case
Infectious mononucleosis	1 case	Entero-colitis	1 case
Encephalitis	1 case	Miscellaneous, used prophylactically, gun-shot wounds, multiple abrasions, lacerations	11 cases
Peri-nephritic abscess	1 case		
Totals	151 cases	Totals	149 cases

* Explanation of terms "Toxic" and "Atoxic" appears in text.

Among these thirty patients, sixteen exhibited side effects sufficiently severe to cause drug discontinuance. These cases are summarized in Table 3, which shows that thirteen (73 per cent) were included in the "toxic" group with but three (27 per cent) being classified as "atoxic." This finding would seem to be not at all inconsistent with the 83 per cent incidence in the otherwise toxic and the 17 per cent incidence in the nontoxic individual as was found in the entire thirty patients experiencing any degree of side effect.

Table 3 also shows that the thirteen "toxic" individuals received sulfathiazole for an average of 5.1 days, as against 9 days for the three "atoxic" patients. Total average dosages for the thirteen "toxic" people was 20.3 gm., as contrasted with an average of 30 gm. for the "atoxic." Again we feel that these calculations are not dissimilar from those found in the entire thirty patients exhibiting side effects.

It is true that Table 3 reveals an average daily dosage of 3.9 gm. of sulfathiazole for the thirteen "toxic" people as against 3.3 gm. for the "atoxic," but it is felt that this difference of less than 1 gm. in the average total daily dosage could hardly account for an incidence of sulfathiazole side effects several times greater in the "toxic" than in the "atoxic" person, particularly since in these sixteen patients the "atoxic" received sulfathiazole on an average of almost four days (80 per cent) longer than did the "toxic." This seems especially pertinent since numerous observers[6] have stated from experimental and clinical observations that prolonged administration of sulfathiazole seems to be a most important factor in

Excessive vomiting seems to occur most frequently early in the course of sulfathiazole administration, and in the cases here cited, this happened in all but one instance. The exception was Case 1 in Table 3. If all early cases of excessive vomiting are excluded from the sixteen cases under discussion, there remain eleven patients, eight in the "toxic" and three in the "atoxic" groups, with a resultant incidence of almost three times the side effects in the "toxic" as in the "atoxic" people. We can find no possible standpoint, but that the incidence of sulfathiazole side effects is much greater in the "toxic" than in the "atoxic" individual. In fact, if we were to eliminate all so-called "atoxic" cases from our series we would be left with 149 "toxic" individuals with an incidence of 25 patients (16.55 per cent) showing undesirable drug effects, a figure very close to that of Pepper and Ham[8] whose entire series we would classify as "toxic."

DISCUSSION

Clinical findings have been presented from 300 patients given sulfathiazole, in support of a premise that undesirable drug side effects occur more frequently in patients obviously toxic and febrile from their illness, than in those individuals whose disease is unaccompanied by such systemic effects. A review of available literature reveals certain evidence tending to support this contention.

The incidence of sulfathiazole intoxication has been recorded in several series of cases, such as those of Fletcher, Gibson, and Sulkin[3] and Culp,[3] who have reported in the first instance,

women, and in the second, men, treated for gonorrhea, with sulfathiazole. The incidence of drug side effects was 6.7 and 6.9 per cent respectively in those two series. It seems reasonably safe to assume that the majority of the cases in both of these series represented people we would classify as "atoxic." In contrast, others have recorded an incidence of sulfathiazole reaction in groups of cases composed of patients, all or for the most part, of a type classified by us as "toxic." Among these writers are Carrol, Kappel, and Lewis[8] who found a 15 per cent incidence of side effects; Reinhold, Flippin and Schwartz[8] who reported 15.6 per cent occurrences; Volini, Levitt and O'Neil,[3] who recorded 11 per cent; and Pepper and Ham[8] who gave a figure of 18 per cent, and others.[3] Comparison between the findings of the first two and the last six observers would seem to show a higher incidence of sulfathiazole side effects in the person already toxic from his disease.

TABLE 2.—*Type of Side Effects and Group in Which They Occurred*

	"Toxic"	*"Atoxic"*	*Total*
Nausea and vomiting	18	2	20
Fever from drug...	2	3	5
Dermatitis	1	0	1
Dermatitis and drug fever	1	0	1
Agranulocytosis ...	1	0	1
Conjunctivitis, and nausea and vomiting	1	0	1
Cyanosis, and nausea and vomiting	1	0	1
Deaths	0	0	0
Totals	25 (8.35%)*	5 (1.65%)*	30 (10%)†

* Percentages represent incidence in entire 300 cases. Expressed as the incidence among those showing sulfathiazole intoxication they would be 83.5% and 16.5% respectively.

† This table shows thirty patients experiencing a total of thirty-three side effects, two each occurring in three different "toxic" patients.

The recent interesting and instructive presentations of Lederer and Rosenblatt,[7] and Merkel and Crawford[8] also deserve comment. Each of these reports cite four deaths apparently attributable to sulfathiazole medication. It was of interest to note that three of the deaths (75 per cent) in the first report occurred in people we would classify as "toxic," while all four patients in the second were apparently toxic from disease although not all were febrile.

If there be any basis of fact for the contention we advance, a reason should be forthcoming. We believe such a reason exists, at least to some extent, in the presence of two factors, in one instance, contributing to the total toxicity of the patient; i.e., drug plus disease toxicity; while in the other but one factor would seem important; i.e., the drug toxicity alone.

To quote MacCallum,[5] further, "when injury is intense enough, poison may be absorbed from the injurious agent or even from dead tissue to affect the nervous system and other organs, and to cause disturbance of their functions and what we know as illness. Even the fever itself may bring along with it disturbances in function." It therefore seems reasonable to say that those patients we have classified as "toxic" had some disturbances in the functions of various organs including the liver and kidneys.

Many observers[9] have pointed out that sulfathiazole is a drug which can and does cause more or less damage in both experimental animals and man, to various organs, including the liver and kidneys; while others[10] have emphasized the importance of proper kidney function during the course of sulfathiazole administration. Reinhold and his coworkers[3] have established that orally administered sulfathiazole in man is excreted up to 93 per cent by the kidneys, a finding supported by the work of Carrol, Kappel and Lewis;[8] while

TABLE 3.—*Patients Exhibiting Severe Sulfathiazole Side Effects, Necessitating Drug Discontinuance*

No. Diagnosis	*Days Drug* Administered*	*Grams of Drug†*	*Reaction Experienced*	*Group*
1. Epididymitis	7	17 gm.	Excessive nausea and vomiting 7th day	"Toxic"
2. Lobar Pneumonia	3	16 gm.	Cyanosis and excessive nausea, vomiting	"Toxic"
3. Lymphadenitis	8	16 gm.	Fever from drug	"Toxic"
4. U.R.I.	2	10 gm.	Excessive nausea and vomiting, early	"Toxic"
5. U.R.I.	2	4 gm.	Excessive nausea and vomiting, early	"Toxic"
6. Broncho-pneumonia	4	22 gm.	Agranulocytosis	"Toxic"
7. U.R.I.	4	15 gm.	Conjunctivitis, nausea and vomiting	"Toxic"
8. Broncho-pneumonia	3	14 gm.	Excessive nausea and vomiting, early	"Toxic"
9. Broncho-pneumonia	10	39 gm.	Dermatitis, and fever from drug	"Toxic"
10. Encephalitis	2	9 gm.	Excessive nausea and vomiting, early	"Toxic"
11. Lobar Pneumonia	12	56 gm.	Fever from drug	"Toxic"
12. P.O. Abdominal	2	9 gm.	Excessive nausea and vomiting, early	"Toxic"
13. Broncho-pneumonia	7	37 gm.	Dermatitis	"Toxic"
14. Localized abscess	9	32 gm.	Fever from drug	"Atoxic"
15. Otitis media, Chr.	10	38 gm.	Fever from drug	"Atoxic"
16. P.O. Orthopedic	8	20 gm.	Fever from drug	"Atoxic"

* Average length of administration: "Toxic" 5.1 days; "Atoxic" 9 days.

† Average total sulfathiazole dosage: "Toxic" 20.3 gm.; "Atoxic" 30 gm.
Average daily sulfathiazole dosage calculated from above: "Toxic" 3.9 gm.; "Atoxic" 3.3 gm.

It is felt that the evident variance in sulfathiazole side effects reported in previously published articles could be explained, at least in part, by the lack of division into "toxic" and "atoxic" cases. in these same reports the first workers state that transitory depression of kidney function occurs in nearly all patients receiving sulfathiazole, and the second express a belief that fear of accumu-

lation of the drug to dangerous levels is negligible except in those cases showing kidney deficiency, and yet it would appear from the work of Reinhold, et al,[3] that the drug itself contributes, at least to some slight extent, to such deficiency. It thus seems that a vicious cycle affecting kidney function may be established. Fortunately, demonstrable kidney damage was not prominent in our 300 cases, although sulfathiazole crystalluria was demonstrated in 32 per cent of them.

Two years ago, Long, et al[11] stated a belief that kidney disturbances following sulfapyridine or sulfathiazole administration might be due to either a true toxic injury to the tubules of the kidney, probably similar to that seen in mercury bichloride poisoning, or it may be due to the deposition of acetylsulfapyridine or acetylsulfathiazole crystals in the kidney tubules, and on occasion to the blocking of the renal pelves and ureters by calculi composed of acetylsulfapyridine or acetylsulfathiazole.

It now seems apparent that most, if not all, kidney damage from sulfathiazole may be due to crystal deposition in that organ. We are aware of apparently important work now in progress by Sobin,[12] which tends to confirm this view.

Reduction of renal function by both the disease and the drug may conceivably decrease excretion of the drug and thus contribute an additional factor which could contribute to the greater incidence of intoxication in febrile patients.

As a part of this same combination, Martin, and his coworkers,[13] have recently shown that the liver is important in the detoxification of sulfonamide compounds and have presented considerable work in attempting to find a means to assist in the detoxification of those drugs. Considerable evidence[14] is at hand to show that sulfathiazole may have a deleterious effect on that organ resulting in impaired liver function and possible reduction in its detoxicating ability.

No mention has been made in this discussion of side effects occurring from other sulfonamides, since our experience has been restricted almost entirely to sulfathiazole. However, it seems reasonable to assume that other similar drugs might be capable of producing the same phenomena.

SUMMARY AND CONCLUSIONS

The incidence of sulfathiazole side effects in 300 otherwise, young, vigorous soldiers has been cited.

These patients have been divided into a toxic, febrile group, called "toxic," by us for descriptive purposes, and into a second group, nontoxic from their disease, called by us, "atoxic."

The distribution of patients in each group was almost equal in number, with no difference in the average age.

The total incidence of sulfathiazole intoxication in the 300 cases was 10 per cent. There were no deaths attributable to the drug.

Sulfathiazole side effects occurred five times more frequently in the "toxic" group than in the "atoxic," or an incidence of 8.35 per cent for the "toxic," and but 1.65 per cent for the "atoxic."

The hypothesis has been advanced that the combination of effects from disease and drug, affecting sulfathiazole elimination and detoxication can account for the larger number of drug reactions found among the "toxic" patients.

Gross kidney involvement in this series of cases was not evident. No reasons can be advanced for this occurrence, except for excellent nursing care given, and the administration of sufficient fluids during drug therapy.

The occurrence of sulfathiazole side effects reported in other series of cases differ widely. It is suggested that this considerable variance might not exist to such a great extent had previous series been reported as, or had they been divided into "toxic" and "atoxic" cases.

Since we have shown clinically that sulfathiazole intoxication occurs as much as five times more often in the toxic, febrile as in the nontoxic patient, this fact should be kept in mind during the administration of all sulfonamides. This is not to be construed in any sense as an argument against the use of any sulfonamide therapeutically indicated.

Station Hospital, Camp Haan,
Riverside County.

REFERENCES

1. Lyons, R. H., and Balberor, Harry: Febrile Reactions Accompanying the Readministration of Sulfathiazole, Journal of the American Medical Association, 118:955-958 (Mar. 21), 1942.

2. Nelson, Jack: Acquired Sensitivity to Sulfonamide Drugs, Journal of the American Medical Association, 119:560-561 (June 13), 1942.

Rantz, Lowell A.: Sulfonamide Medication, California and Western Medicine, 56:347-350 (June), 1942.

3. Fletcher, Paul F., Gibson, Ora J., and Sulkin, S. Edward: Sulfathiazole in the Treatment of Gonorrhea in Women, Journal of the American Medical Association, 117:1769-1773 (Nov. 22), 1941.

Culp, Ormond S.: Treatment of Gonorrhea with Sulfathiazole, The Journal of Urology, 44:367-376 (Sept.), 1940.

Carroll, G.: Kappel, L., and Lewis, B.: Sulfathiazole; A Report on Clinical Investigations, Journal of the American Medical Association, 115:1350-1353 (Oct. 19), 1940.

Reinhold, John G.: Flippin, Harrison F., and Schwartz, Leon: Observations on the Pharmacology and Toxicology of Sulfathiazole in Man, American Journal of the Medical Sciences, 199:393-401 (Mar.), 1940.

Volini, I. F., Levitt, R. O., and O'Neil, H. B.: Cutaneous and Conjunctival Manifestations of Sulfathiazole Intoxication, Journal of the American Medical Association, 116:938-940 (Mar. 8), 1941

Pepper, D. S., and Ham, G. C.: Sulfathiazole Treatment in Respiratory Infections, American Journal of the Medical Sciences, 200:784-790 (Dec.), 1940.

Finland, M., Lowell, F. C., and Strauss, E.: Some Aspects of the Chemotherapy of Pneumonia, New York State Journal of Medicine, 40:1115-1122 (July 15), 1940.

Cutts, M., Burgess, A. M., and Chafee, F. H.: The Treatment of Lobar Pneumonia with Sulfathiazole and Sulfapyridine, New England Journal of Medicine, 223: 762-764 (Nov. 7), 1940.

4. Hendricks, Coleman B.: Sulfonamide Compounds: Blood Changes Therefrom, California and Western

(References Continued on Page 89)